REMARKS

Claims 81, 82, 86, 87, 92, 94, 96-98, 102 and 103 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicant as his invention. In amending Claims 81, 82, 86, 87, 92, 94, 96-98, 102 and 103 to focus with more particularity and clarity on one aspect of the invention as originally filed, Applicant respectfully reserves the right to file subsequent application(s) to protect the invention commensurate with the scope as originally filed.

Claims 81, 82, 94, 96-98, 102 and 103 have been amended to replace "wild-type" with "full-length", with reference to subject proteins. Support for that amendment can be found throughout the instant specification, particularly at the passage beginning at page 3, line 3, which reads:

> Representative immunoassays are disclosed which are used to screen primarily for certain types of hereditary colorectal cancer (CRC) or a predisposition to hereditary CRC. Such representative immunoassay methods to screen for hereditary CRC or a predisposition thereto are based on the detection of cellular full-length protein level changes that are due to either (1) mutations of the adenomatous polyposis gene (APC), a mutation that is associated with familial adenomatous polyposis (FAP), or to (2) mutations of mismatch repair (MMR) genes, particularly, MLH1, MSH2, PMS1, PMS2, and MSH6, mutations that are associated with hereditary non-polyposis colon cancer (HNPCC).

[Specification at page 3, lines 3-11; emphasis added.] Further particular support can be found in the specification at least at page 1, lines 9-12; at page 2, lines 24-29; at page 6, lines 7-9; at page 7, lines 6-9; at page 9, line 22 to page 10, line 2; at page 12, lines 14-19; at page 14, lines 18-19; at page 15, line 31 to page 16, line 1; at page 19, line 27 to page 20, line 3; at page 23, line 31 to page 24, line 2; at page 27, line 10 to page 28,

line 2; at page 29, line 19 to page 30, line 14 (APC); at page 31, lines 6-12; at page 38, line 10 to page 39, line 15 (MLH1 and MSH2); and at page 45, line 21 to page 59, line 20 (Examples 1-4).

Claim 86 has been amended for greater clarity and particularity to specify that the biological sample of "body fluids" is one "containing cells", and Claim 87 has been amended to delete "serum" as a candidate body fluid. Support for biological samples containing cells can be found in the specification at the least at page 11, line 5, wherein the first method step in the exemplary immunoassay methods is specified as "(a) isolating a sample of normal cells from said organism"; and at page 12, lines 6-10, which reads:

> Preferred biological samples are cell samples, cell extracts, cell lysates, supernatants from cell lysates, tissue samples and tissue extracts. Further preferred are normal cell samples, normal cell extracts, lysates of normal cells, and supernatants of normal cell lysates. Particularly preferred are samples of peripheral blood lymphocytes (PBLs), lysates of PBLs, supernatants from lysates of PBLs, and extracts of PBLs.

Claims 81 and 92 have been amended to delete the PMS2 protein as a subject protein for use in the screening assays of the invention.

Applicant respectfully submits that no new matter has been entered by the above amendments.

I. 35 USC 112, 2nd Paragraph Rejection

"Wild-type"

Claims 81-103 stand rejected under 35 USC 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention." [Office Action, page 3, section 5.] Applicant respectfully traverses this rejection, pointing out that the amendments to Claims 81, 82, 94, 96-98, 102 and 103 replacing "wild-type" with "full-length" (with reference to subject proteins) overcome the instant rejection. Applicant further respectfully points out, as detailed above in the Remarks section, that the instantly claimed methods of screening for hereditary colorectal cancer by quantitating the levels of "full-length subject proteins" are very well supported in the instant specification.

In addition, Applicant respectfully points out that the screening assays of the instant invention would be enabled for "wild-type" subject proteins as well, as antibodies that could distinguish between wild-type and mutant epitopes of subject proteins are known in the art, and could be used in the screening assays.

In view of the amendments to the claims and the above remarks, Applicant respectfully concludes that the claims as amended comply with the requirements of 35 U.S.C. § 112, second paragraph. Applicant respectfully requests that the Examiner reconsider and withdraw this rejection in view of the above amendments and remarks.

II. First 35 USC 112, 1st Paragraph Rejection

"Serum"

Claims 81-103 stand rejected under 35 USC 112, first paragraph because "the specification, while being enabling for bodily fluids that contain cells, does not reasonably provide enablement for bodily fluids that do not contain cells (e.g.,)." [Office

Action, page 3, section 6.] Applicant respectfully traverses, submitting that the amendments to Claims 86 and 87 overcome the instant rejection.

Applicant respectfully points out that the sole independent claim, Claim 81, specifies that the "biological sample" for use in the screening methods is already specified as one "containing normal cells" [Claim 81(a)], but for the purposes of expediting the prosecution of the instant application, Claim 86 has been amended to specify that the body fluid samples are those "containing cells", and Claim 87 has been amended to delete "serum" as a candidate body fluid. As it appears from the Office Action that "serum" is the only body fluid for which the claimed methods are considered not to be enabled, Applicant respectfully submits that the claims as amended comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicant respectfully requests that the Examiner reconsider and withdraw this rejection in view of the above amendments and remarks.

III. Second 35 USC 112, 1st Paragraph Rejection

"PMS2"

Claims 81-103 stand rejected under 35 USC 112, first paragraph, because "the specification, while being enabling for methods for screening for hereditary colorectal cancer . . . , where the subject proteins are selected from the group consisting of MLH1, MSH2, MSH6, PMS1 and APC, does not reasonably provide enablement for where the subject proteins include PMS2." [Office Action, page 4, section 7.] Applicant respectfully traverses, submitting that the amendments to Claims 81 and 92 overcome the instant rejection.

Claims 81 and 92 have been amended to delete the PMS2 gene as a subject protein for use in the screening assays of the invention. However, Applicant respectfully points out that the cited Gill et al. reference [Clin. Cancer Res. 11(18): 6466-6471 (2005)] actually **supports** the enablement (and utility) of screening assays where PMS2 is a subject protein: "[L]oss of PMS2 expression . . . is present in 72% of cases of colorectal tumors . . . in which there is retention of normal expression of MLH1, MSH2, and MSH6 DNA mismatch repair gene products." [Gill, page 6468, last paragraph; emphasis added.] If **serial** screening assays were performed (for example, a first screening assay measuring MLH1 and MSH2 protein levels, followed by a second screening assay measuring PMS1 and PMS2 protein levels if the first assay indicated normal levels), the inclusion of PMS2 as a subject protein in immunological screening assays might be the only practical method to detect PMS2 mutations as a cause of hereditary colorectal cancer. Based on the results of Gill et al., if a first MLH1:MSH2 assay showed normal protein levels, the second PMS1:PMS2 assay would have a 72% probability of detecting a loss of PMS2 expression, if the colorectal cancer has a high level of microsatellite instability (MSI-H). That **serial assay** embodiment of the invention is supported in the specification at the least at the passage beginning at the bottom of page 23: "Moreover, immunoassays of this invention to detect full-length PMS1 and PMS2 protein in conjunction with the MLH1 and MSH2 assay would significantly reduce the numbers of MMR mutations not identified." [Specification, page 23, line 31 to page 24, line 2.] There is nothing in Gill et al. to indicate that loss of PMS2 expression correlates with loss of PMS1 expression, and one of skill in the art would know that the

screening assays would be used only to compare levels of mismatch repair proteins that are not lost in concert, and choose subject proteins accordingly.

Applicant respectfully submits that the claims as amended comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. Applicant respectfully requests that the Examiner reconsider and withdraw this rejection in view of the above amendments and remarks.

CONCLUSION

Applicant respectfully concludes that the claims as amended are in condition for allowance, and earnestly requests that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference could be helpful, the Examiner is invited to telephone the undersigned Attorney for Applicant at (415) 981-2034.

Respectfully submitted,

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